Dyspnea

IN THIS ISSUE OF THE Journal, O’Donnell et al. (10) report the intensity of dyspnea experienced by patients with chronic obstructive pulmonary disease exercising at 75% of their incremental maximal working capacity. The rationale for the study was as follows: sensation begins with a stimulus that acts on a sensory receptor and is relayed to the central nervous system, where it is interpreted in light of previous experience and learning. A single stimulus, several stimuli in an additive manner, or an interrelationship between stimuli generates discomfort in the act of breathing. Measurements of O₂ uptake, CO₂ production, end-tidal CO₂ pressure, arterial O₂ saturation, the capacity of the respiratory muscles to generate pressure, the inspiratory and expiratory esophageal pressure, operating lung volume, ventilation, breathing pattern, and respiratory timing were referenced alone and in combinations to the subjective ratings of dyspnea. A compound stimulus arising from inappropriateness between the motor output and the displacement achieved because of hyperinflation and restriction in volume expansion was forwarded as the cause of dyspnea in these patients.

Labored breathing has been linked to dyspnea for over 2,000 years because exertional discomfort is experienced with the intense activation of all peripheral skeletal muscles. Awareness of the intensity of the central motor drive was introduced by natural philosophers in the 1600s as a logical explanation for our appreciation of exertional effort (for review see Ref. 2). The sense of effort was formally adopted in physiological circles by Müllner (7) in the nineteenth century to complement his specific energy of nerves (i.e., specific nerves carry specific sensations). Helmholtz (6), his most eminent pupil, proved that we are aware of the motor activation of the extracocular muscles of the eye before movement is achieved, explaining the stability of the visual field. Over the succeeding years, awareness of the outgoing motor command was seen to be accompanied by an appreciation of its achieved effects as the intramuscular receptors became known, i.e., a sense of tension arising through tendon organ stimulation, a sense of movement and position through the stimulation of muscle spindles and joint receptors, and a sense of focal discomfort and pain through the stimulation of intramuscular free nerve endings.

The responsiveness of muscle to its centrally generated motor command declines rapidly at high power outputs and more slowly as power decreases. This process is known as fatigue. The motor command accompanied by the sense of effort intensifies as power increases and to sustain the same power as the duration of activity increases. Perceived exertion intensifies with the power generated and with the duration of activity in an interactive manner: Effort = constant × Power² ×Duration⁰.² (8). Doubling the power output increases the sense of exertional effort by fourfold; doubling the duration of activity increases the sense of effort by 15%. Hence the same work can be performed with less effort by reducing power and increasing the duration of activity. Exercise is voluntarily terminated when the subject is no longer willing to tolerate the exertional discomfort due to increasing power or increasing the duration of either the respiratory or peripheral skeletal muscles. The average subject stops exercise when the intensity of exertional effort reaches “severe” (5) to “very severe” (7) on the Borg scale (0–10).

The effort-power relationship is a fundamental construct. The responsiveness of muscle to its motor command is integrated with the neuromotor, circulatory, respiratory, muscular, and metabolic systems. The responsiveness of muscle to motor drive declines if the availability of substrate, oxygen delivery, carbon dioxide excretion, homoeostasis in electrolyte, and acid-base status are compromised. Common examples are as follows: under hypoxic conditions, increased effort is required to sustain power as evidenced by the profound fatigue noted during exercising at altitude; with shock, increased effort is required to sustain power as also evidenced by profound fatigue noted with reduction in muscle blood flow.

In this study patients with chronic obstructive pulmonary disease were required to sustain 75% of their incremental maximal power to toleration. Respiratory effort is traditionally measured using ventilation referenced to maximal breathing capacity. An alternative estimate of respiratory effort was made using the following assumption. Maximal volitional effort leads to maximal force as evidenced by the interpolated twitch technique, which discloses close-to-maximal motor unit activation. Force per maximal force was used to estimate respiratory effort. There were limitations to the approach. Referencing ventilation to maximal breathing capacity is flawed because maximal breathing capacity measured over 15 s declines to ~70% when measured over 4 min. The power duration curve applies to all muscles. Force referenced to force-generating capacity over a single maximal resting contraction has the same limitation. A further limitation arises because the force available to inspire declines as the length of the muscle decreases as lung volume expands (length-tension relationship) and as the velocity of contraction increases with inspiratory flow (force-velocity relationship). Esophageal pressure was not referenced to the maximal pressure, allowing for the changing length and velocity of contraction. The pressure generated across the lungs was measured in the esophagus representing the pressure required to overcome resistance (R = P/V˙) and elastance (P/V) of the lung: P = VE + V˙R. Unfortunately volume and flow contribute simultaneously reduce the capacity to generate force. In young healthy men, the maximal inspiratory pressure at functional residual capacity (FRC) is ~120 cmH₂O and declines to 40 cmH₂O during a maximal inspiration to total lung capacity and from 120 to 40 cmH₂O at FRC with an increase in flow rate of 8–10 l/s at FRC (9). The transpulmonary and transthoracic pressures, maximal inspiratory and expiratory pressures, operating lung volume, and flow rate all independently contribute to effort. These are no formal accepted standards for measuring effort.

One might cogently argue that the respiratory and leg muscles fatigue at 80% of maximal power on a cycle ergometer. As indicated by the psychophysical equation outlined above, an increasing effort is required to breathe and cycle during sustained cycle ergometry in normal subjects at much lower power outputs. The increasing intensity of leg effort and dyspnea as the forces generated are sustained are sensitive manifestations of fatigue. Methods of measuring the onset and progression of fatigue during sustained activity are relatively insensitive. A
study design including sustained exercise at several power outputs such as that described in normal subjects would have provided a more convincing result.

Acute respiratory failure generates a very unpleasant urge to breathe: “breathlessness,” a sensation familiar to all who have ever held their breath (1, 5). An increasing arterial PCO2, a declining arterial PO2, and acidemia provide the stimulus for this sensation. Breathlessness recedes over time as patients with chronic respiratory failure adapt. Breathlessness returns with acute on top of chronic failure. Dyspnea recedes over time in a similar manner as long as the muscle do not fatigue. Dyspnea reappears rapidly with the increasing respiratory effort associated with exercise. Respiratory failure was not seen in these patients and breathlessness was not expected. Confusion between dyspnea characterized by exertional effort and breathlessness characterized by respiratory failure is common. In most patients behavioral learning ensures that the power generated during exercise is sufficiently low so that respiratory failure and breathlessness are avoided.

In 1963 Campbell and Howell popularized the idea that humans are especially aware of any sudden inappropriateness between effort, force, and displacement; inappropriateness in length-tension relationships results from the addition of small resistive and elastic loads that are not particularly distressing (3). Inappropriateness in the effort required to generate force and ventilation with acute hyperinflation leads to neuromechanical inappropriateness. However, the effort contributed to increasing discomfort over time. The limited expiratory airflow capacity at low lung volumes limited the capacity to breathe within the confines of the inspiratory flow capacity at these volumes in these patients. Hyperinflation increased the capacity to expire, increasing the capacity to breathe with the added cost of increased inspiratory effort. Inappropriateness between effort, length, and tension certainly alerts patients to a problem, but the distress continues to increase with effort.

The static pressure-volume diagram bracketed by the capacity of the respiratory muscles to generate pressure was first introduced in the 1920s by Rohrer (11) and rediscovered in the 1950s by Otis et al. (10). Flow-resistive pressures add to the demands while reducing the capacity to generate force with increasing flow and velocity of muscle contraction. The forces required to breathe during the present study should be bracketed by the capacity of the respiratory muscle to generate force. Dyspnea subjectively measured should be addressed within this framework. A simpler alternative arose with the introduction of the maximum inspiratory and expiratory flow volume curve by Fry and Hyatt (4). A quantitative analysis of the tidal flow-volume loops relative to the maximal flow volume envelope over the same volume excursion gives a measurement of respiratory effort. Any reduction in the maximal flow-volume area following activity implies either a reduction in force-generating capacity (i.e., fatigue) or an increase in the forces opposing muscle contraction.

Where are we going? This manuscript bridges the boundaries between respiratory physiology, neurophysiology, symptoms, and clinical medicine. Given the broad nature of the study, it is not surprising that complexity was found. The results could be interpreted in several different ways. The same receptors must be stimulated during exercise in normal people and in the presence of cardiorespiratory and neuromuscular diseases. Inappropriateness between the motor output, force generated, and volume displaced reaches consciousness, often causing patients to seek help. Discomfort undoubtedly intensifies with the effort required to breathe and cycle. Breathlessness undoubtedly arises with respiratory failure. There may be even further additional sources of discomfort. Psychophysical studies should be increasingly added to classical respiratory physiology, elucidating how discomfort is generated in the act of breathing. The questions addressed in this study reaffirm the need for a Journal of Applied Physiology to resolve confusion in the area of both physiology and medicine.

REFERENCES

7. Müller JP. Elements of Physiology. Thoemmes Continuum, 1846. [transl. by Baly W.]

Kieran Killian
McMaster University
Ontario, Canada
e-mail: killian@mcmaster.ca